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J.B. WOLFFE MEMORIAL LECTURE

Is the lung built for exercise?

JEROME A. DEMPSEY

John Rankin Laboratory of Pulmonary Medicine,
Department of Preventive Medicine,
University of Wisconsin,
Madison, WI 53705

HYPOTHESIS

The working hypothesis which serves as the theme for this paper is illustrated in Figure 1 and may be summarized as follows. On the one hand, the pulmonary system is ideally designed and regulated to meet the homeostatic demands of even very heavy short term exercise in a normal, healthy young adult. Thus exercise capacity or at least maximum $\dot{V}O_2$ is determined by "weaker links" in the chain of oxygen transport and utilization such as maximum stroke volume, cardiac output, skeletal muscle vascularity, and/or oxidative capacity of locomotor skeletal muscles (46, 47). However, this hierarchy of "limiting" factors changes as one progresses up the fitness continuum so that the gas exchange capability of the lung and/or the maximum responsiveness of the chest wall and ventilatory control system now assume a more critical, rate limiting step in determining maximum oxygen consumption. This reordering of exercise performance determinants occurs because the trained state is achieved by increased output capacities of the cardiovascular system and greatly enhanced metabolic capacities of locomotor muscles. The pulmonary system, however, remains largely unchanged from its original, once dominant state, and thus eventually the point is reached where its capacity for gas transport no longer exceeds (and eventually is even less than) that of the other "adapted" organ systems. I will now examine data and concepts which speak to each of these proposals. Some aspects of this hypothesis have been examined in recent reports (14, 17).

THE ARCHITECTURE AND REGULATION OF THE HEALTHY, UNTRAINED PULMONARY SYSTEM IS IDEALLY SUITED FOR EXERCISE!

Proposed regulatory scheme. I will concentrate here on the normal untrained person capable of exercise levels which reach 3–3.5 $l \cdot min^{-1}$ or 40–50 $ml \cdot kg^{-1} \cdot min^{-1}$, $\dot{V}O_{2max}$. Demands on the ventilatory system are substantial under these conditions, because to meet the increased metabolic demands sustained increases in both inspiratory and expiratory flow rates must be accomplished in much shorter periods of time. The result is quite remarkable because not only is an adequate ventilatory response achieved and arterial blood gas and acid-base status fairly well protected, but the major determinants of mechanical impedance of the lung, i.e., resistance and compliance, remain essentially unchanged. Indeed, we rarely even sense an increased breathing effort during exercise until flow rates and minute ventilation exceed at least 8–10 times the resting values.

This combination of homeostasis plus efficiency requires a multi-faceted control system which will not only generate neural output from the brain stem respiratory neurons appropriate to the metabolic demand of the exercise but will also ensure the efficient transformation of this neural "drive" into mechanical output from the lung in the form of precisely augmented airflow and alveolar ventilation. The required sequence of events is depicted in Figure 2. Note that there are two types of feedback: 1) a well known chemical or chemoreceptor-linked feedback which corrects any "errors" in ventilatory response so as to insure fairly well regulated arterial blood gases and cerebral fluid acid-base status; and 2) a less well appreciated and understood "mechanoreceptor" type of feedback system which seems to sense some variable related to the amount of work expended in taking a breath, such as the amount of tension developed by the respiratory muscles *or* the amount or rate of stretch of parenchymal tissue *or* the pressures developed in the airways. Appropriate receptors for these stimuli are in place in lung parenchyma, airways, and in the muscle spindles and tendon organs of intercostal muscles and diaphragm. In turn the sensory information affects the output of both spinal motor neurons directly or brain stem respiratory center neurons to govern breathing pattern, the force of respiratory muscle contraction, and even the pattern of recruitment of respiratory muscles.

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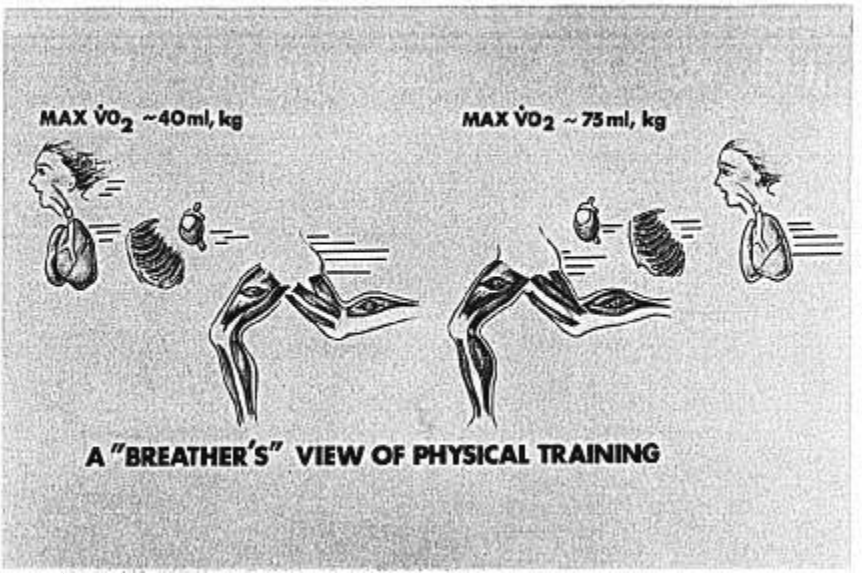

Figure 1—Hypothesis: In the untrained the capacity for O_2 transport by the pulmonary system (lungs and chest wall) far exceeds that of the cardiovascular system and the oxidative capacity of the limb locomotor muscles. Physical training primarily causes adaptation in the skeletal muscles and in the systemic cardiovascular system, with little change in the pulmonary system. Thus, eventually the capacity of the pulmonary system for O_2 transport cannot meet the superior demands imposed by the limbs and cardiovascular systems; arterial blood gas and acid-base homeostasis fail and the lungs become a significant limitation to performance capacity.

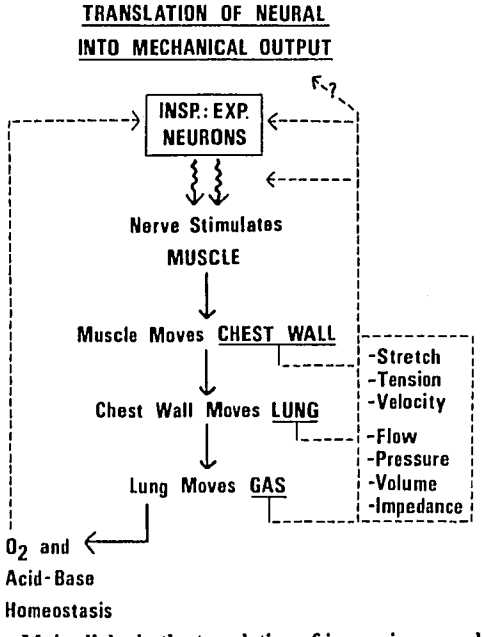

Figure 2—Major links in the translation of increasing neural output from the brain stem (which could occur from any stimulus to breathe such as acidosis or the increased drive associated with the controversial primary exercise hyperpnea stimulus) to gas flow at the airway opening. Feedback pathways are shown from medullary and carotid chemoreceptors on the left and from "mechanoreceptors" in the lung and chest wall on the right. The types of pulmonary receptors include: 1) those in the airways with feedback to brain stem (and perhaps higher CNS) via the vagus nerve; and 2) the muscle spindles and tendon organs in respiratory muscles with efferent pathways in the phrenic nerve and spinal cord. Some of the suspected "signals" which might activate these mechanoreceptors are listed.

There are a number of examples of responses to exercise which support these concepts of ventilatory control outlined in Figure 2 and the "minimum work" hypothesis. We will examine just a few (also see Refs. 37, 40, 43, and 51).

Importance of lung and airway mechanics in ventilatory control. The relationships of tidal volume to breathing frequency (or rates of airflow) are carefully controlled so that at moderate work levels $\dot{V}_E$ increases primarily due to the tidal volume response, and at higher work rates tidal volume tends to plateau at about 65% of the vital capacity, and increases in breathing frequency become the major contributor to further increases in $\dot{V}_E$. Thus tidal volume (V_T) increases by encroaching on both inspiratory and expiratory reserve volume (also see below) so that the relationship between transpulmonary pressure exerted on the lung and lung volume change remains on the linear, efficient portion of the pressure:volume relationship (18). There are, of course, also limits to changes in breathing frequency and to airflow rates, especially during expiration where the airways can be "dynamically" compressed, as the tethering action which tends to hold intrathoracic airways open is removed at lower lung volumes and the intrapleural pressure outside the airway exceeds the intra-luminal pressure. These limits are not encroached upon by the demands for airflow and pressure development experienced during even maximum exercise in healthy, untrained persons.

A simple experiment comparing voluntary and involuntary hyperpnea illustrates how sensitive the feedback control system is to excessive efforts in the face of inappropriate pressure development. In Figure 3, a typical breath during voluntary ventilation efforts is compared to one achieved during heavy exercise; note that about equal peak inspiratory and expiratory rates of air flow are achieved in both conditions. Pressure development in the expiratory phase of heavy voluntary ventilation exceeds the maximum "effective pressure;" i.e., most of the effort development is against a compressed airway and is therefore not providing any further flow, whereas during exercise, the same expiratory

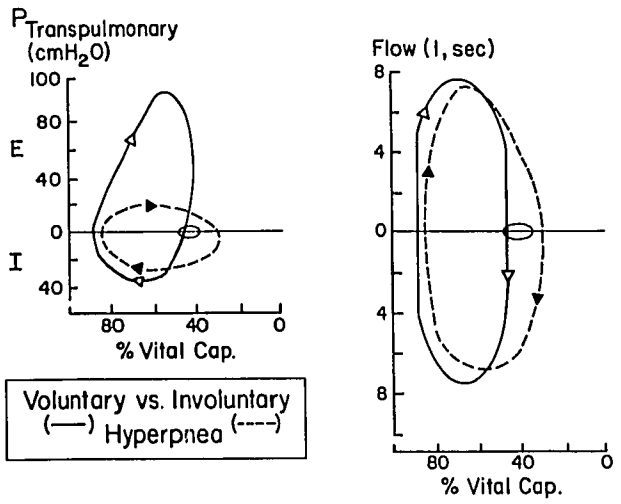

Figure 3—A simple demonstration that the work expended to produce a near-maximum flow rate when breathing is involuntarily controlled may be substantially less than when breathing is voluntarily controlled. On the right are shown three flow:volume loops from atypical breaths obtained in each of three states—quiet breathing at rest, maximum voluntary ventilation at rest, and near maximum exercise, with the latter two accomplished at about equal flow rates but at a higher FRC in the voluntary hyperpnea. On the left are the corresponding pressure:volume loops. The transpulmonary pressures at which dynamic compression of airways could be expected to occur during expiration approximate 40 to 20 cm H_2O over the corresponding lung volume range of 80 to 40% of vital capacity. These pressures are greatly exceeded during voluntary but not involuntary hyperpnea.

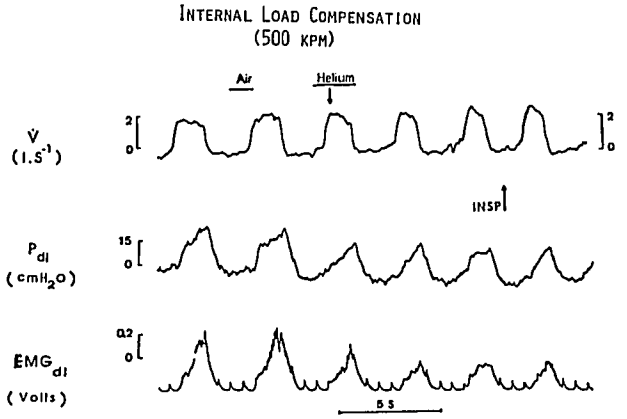

Figure 4—Effects of reducing airway resistance during mild exercise on respiratory neural output to the diaphragm (integrated diaphragmatic EMG). The subject was turned into the warmed and humidified 0.80 He:0.20 O_2 mixture during expiration. Airway resistance fell about 40% on the subsequent inspiration (↓), and this is reflected (in part) by the reduced pressure development across the diaphragm (Pdi). The coincident reduction in EMG_{di} means that the reduced "load" or need for tension development was "sensed" probably by respiratory muscle proprioceptors, and the respiratory motor output was reduced accordingly.

flow is produced but at substantially less pressure and effort, as all pressure production is associated with coincident increases in flow. Somehow in achieving a given flow rate the development of "excessive," wasteful pressure or effort by the respiratory muscles is sensed and therefore avoided in the spontaneously regulated control system; this efficiency is apparently overridden when the cortex exerts voluntary control over this pressure development. This example also illustrates the caution required in using the results from tests under purely volitional control (such as the maximum voluntary ventilation test) to make any inferences about physiological states (such as exercise) (32).

Recent data also demonstrate that the control of exercise hyperpnea includes a significant input from attempts to compensate for the mechanical "load" presented by even the normal mechanical impedance of the lung (35). This sensitivity of the control system to pressure or tension development by the respiratory muscles was demonstrated in mild to heavy exercise by reducing airway resistance, thereby presenting a reduced "load" to the respiratory muscles, by breathing a reduced density gas (He:O_2) (Fig. 4). Within the initial few breaths following this 40–50% reduction in airway resistance, the inspiratory neural "drive" from the CNS to the diaphragm fell substantially, as shown by a 20–40% reduction in the amplitude and rate of rise of the diaphragmatic EMG signal, and the development of transdiaphragmatic pressure was reduced. These changes persisted for the few minutes that He:O_2 was inspired, and air-breathing abruptly restored normal resistance and neural drive. It follows then that in the normal (air-breathing) state the higher EMG activity (or "drive") must be due to some reflex effect which is sensitive to the normally occurring resistive load or impedance presented by the lung to the respiratory muscles. This proprioceptive form of feedback from the lung and/or chest wall is a significant determinant of exercise hyperpnea and of arterial PCO_2 ($PaCO_2$), and its relative contribution increases as exercise intensity, breathing frequency, and pulmonary impedance increase (15).

Respiratory muscle recruitment and fatigue. The recruitment patterns and actions of the respiratory muscles are another critical factor which insures the "minimum work" response to exercise. Basic to this idea is the fact that many muscles are concerned with ventilation production, some of which serve a dual role in such activities as locomotion, speech, posture, and regulation of airway caliber. For example, consider the coordinated integration of muscle actions required for the regulation of expiration during hyperpnea (Fig. 5). At rest, expiratory flow is slowed and expiratory time is prolonged (relative to that attained during purely passive recoil in the paralyzed intubated system) because of two "brakes" on expiratory airflow: 1) the diameter of the extrathoracic airway at the level of the larynx presents a high resistance to airflow; and 2) the antagonistic action of the diaphragm continues to contract during the initial phase of expiration (42, 43). It is postulated that these "brakes" on expiration are important to preserving a pattern of breathing (under resting conditions at least) which best serves the efficient

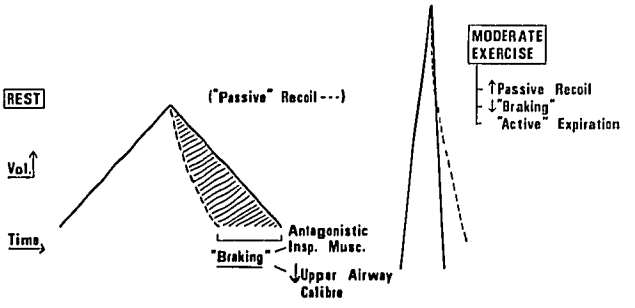

Figure 5—Factors controlling expiratory flow rate at rest and during exercise. The dashed line refers to the time course of expiration if passive recoil was the only determinant of expiratory flow; i.e., the upper airway resistance was removed by tracheal intubation and all respiratory muscles were paralyzed. The solid line (during expiration) refers to the actual time-course of expiration in the intact state (see text for details). In essence, during any hyperpneic state elastic recoil increases, and flow is assisted by active expiration and opposed by any braking action.

generation of the required amount of alveolar ventilation (42). Since ventilatory drive and breathing frequency increase with exercise, the time available for expiration is, of course, greatly reduced, and in order to ensure that expiratory flow is substantially augmented so that expiration will be completed without an extraordinarily high level of expiratory effort, three types of changes probably occur. First, the brakes are reduced as the abductor muscles controlling the laryngeal aperture are activated and the airway diameter is enlarged (20); secondly, elastic recoil is augmented because of increased end-inspiratory lung volume; and thirdly, expiratory muscles in the abdomen and rib cage (intercostals) are now activated. The augmented neural inputs to both the airway and expiratory muscles originate in the brain stem, so in many cases when inspiratory neurons, the phrenic nerves, and diaphragm are all stimulated by the "exercise hyperpnea stimulus," so probably are the motor nerves which activate expiratory muscles and which prepare the airway for increased flow rates (38). The result of these combined actions is that despite the marked reduction in expiratory time during heavy exercise expiratory flow is now increased sufficiently so that not only is end-expiratory volume (i.e., FRC) not elevated, it may actually be reduced substantially below resting levels and resistance to expiratory airflow is maintained near resting levels.

Of course these same principles apply to the control of inspiration whereby flow rates can be greatly augmented with minimal change in airway resistance. Other muscles in the chest wall also provide important assistance to the diaphragm, thereby in effect "sparing" the major muscle of inspiration during exercise. So the major contribution to the increased V_T with exercise is an expansion of rib cage volume or dimensions, probably reflecting a marked augmentation of intercostal muscle activity which acts to both assist directly in lung inflation (i.e., truly agonistic activity) and to stabilize the rib cage to more readily permit its expansion solely through diaphragmatic action. In fact, recent *in vitro* data suggest that the length:tension and force:frequency characteristics of the parasternal intercostal muscles are ideally suited for the predominance of intercostal contributions to augmenting tidal volume and breathing frequency (21). The diaphragm is also indirectly assisted by the abdomen in two ways. First, the abdominal contents act as a fulcrum against which the domed diaphragm can descend, thereby causing the lower ribs to expand and increase rib cage dimensions. Secondly, when active expiration of abdominal and intercostal muscles reduces end-expiratory lung volume (see above) this assists the subsequent inspiration in two important ways: 1) diaphragmatic length is increased and therefore capable of generating increased tension for the same amount of phrenic nerve activation (28); and 2) energy is stored in contracting abdominal muscles which at end-expiration is released and abdominal recoil generates the negative shift in abdominal[1] and thus in pleural pressure to assist lung volume expansion directly at the initiation of inspiration.

Despite the operation of these many and varied "optimization mechanisms," might the ventilatory demands in heavy and/or prolonged exercise exceed pressure generation capabilities of the respiratory muscles causing fatigue to occur? Certainly normal and healthy respiratory muscles will fatigue if they are required to sustain artificially high pressures and abnormal breathing patterns (3)—but we do not know if the combination of factors which determine respiratory muscle energy expenditure, i.e., the magnitude of the pressure development, the frequency of contraction, and the velocity of shortening, are sufficient during even maximum physiological exercise to cause their fatigue. Nor is it known if the demand for energy and thus blood flow solely by the *respiratory* muscles is sufficient to limit the $\dot{V}O_2$ and exercise capacity of *locomotor* muscles during heavy exercise, especially prolonged heavy exercise. Fregosi's data in untrained rats during exhaustive exercise in normoxia and in hypoxia showed a substantial sparing of respiratory muscle glycogen relative to that in limb locomotor muscles of similar

[1] These changes in abdominal pressure may also markedly influence venous return from the legs. For example, when the diaphragm is predominantly active at the initiation of inspiration and its contraction accounts for almost all of the generated tidal volume, then abdominal pressure swings in a positive direction during inspiration, compresses the inferior vena cavae in the abdominal cavity, and reduces venous return from the legs (57). Thus venous return could increase during expiration. However, the increased use of intercostal muscles during inspiration combined with abdominal muscle recoil following active expiration would be expected to markedly change this association between breathing cycle and venous return, because abdominal pressure moves in a negative direction during at least the initial phase of inspiration, and the total (positive) change in abdominal pressure over the whole inspiration is minimized. Whether these effects cause any significant change in *net* venous return to the heart over the *whole* respiratory cycle remains unknown.

fiber type (22). In humans, the few attempts made to date to measure or calculate the energy expenditure or fatigue of respiratory muscles during exercise lack the necessary objectivity and specificity (9, 10). Further, conventionally airway occlusion tests are used to derive indices of muscle performance [such as tension-time index of the diaphragm *or* $\%P_{di}max$ *or* $\%P_{mus}max$ (3, 10, 58)] for purposes of estimating the relative fatigue state of the respiratory muscles during physiological conditions like exercise; but these indices fail to recognize that frequency of contraction as well as velocity of shortening contributes very importantly to the total work and energy expenditure of the muscle (3).

Some qualifiers. I've continually referred to the regulatory scheme (Fig. 2) as one that calls upon a host of feedback and feed-forward mechanisms aimed at optimizing lung, airway, and muscle mechanics so as to minimize the work done by the respiratory muscles. Of course we have no evidence that sensory elements included in this regulatory scheme are in fact aware of the actual amount of mechanical work done by respiratory muscles. It is more plausible that changes in individual quantities are detectable by the different types of receptors, such as stretch by the lung parenchyma, flow or pressure by airway receptors, and tension or length by the muscle spindles and Golgi tendon organs in the chest wall (43). The net effect of all of these types of feedback in combination with neural-humoral stimuli proportional to tissue CO_2 production results in a fairly precise, homeostatic, low-cost exercise hyperpnea.

In addition to the regulatory strategies outlined here, it is obvious that the *structural capacities* of the lung and chest wall were designed to meet the peak needs imposed by muscular exercise. For example, 3+-l tidal volumes in heavy exercise are only made possible because of the 5–6-l vital capacity in the normal adult, and 5–7 $l \cdot s^{-1}$ expiratory flow rates are achievable only because of the inherent diameter and compliance of intrathoracic airways and the elastic recoil properties of healthy lung parenchyma. In addition the respiratory muscles, as the only "essential" skeletal muscles, have biochemical characteristics which appear to be much closer to cardiac than to locomotor muscle. Thus, diaphragm muscle has an oxidative capacity and capillary density which is 2–3 times that in limb locomotor muscles of similar fiber type and demonstrates high uptake and utilization rates of lactic acid during prolonged high intensity stimulation (22, 45, 47).

Alveolar to arterial gas exchange. Finally, we take only very brief note here of the adequacy of alveolar to arterial gas exchange, which is especially dependent upon the reserves provided by the architecture of the pulmonary vascular bed. Simply stated the consistent observation is that in the healthy untrained human working hard at sea level, despite marked reductions in mixed venous O_2 content, and up to 4- to 5-fold increases in pulmonary blood flow: 1) alveolar capillary diffusion distances are maintained; 2) the average transit time of red blood cells through the pulmonary capillaries is maintained within about one-half the resting time; 3) ventilation to perfusion ratios of the lung are high and fairly uniformly distributed; and 4) arterial PO_2 is maintained at resting values. Regulation of these factors has been detailed previously (18); the key factor worth repeating here is that the pulmonary capillary blood volume is capable of expanding to about 3 times its resting value and in a linear fashion with increasing pulmonary blood flow. This is the critical element to insure: 1) a sufficiently long red blood cell transit time for purposes of equilibration of pulmonary capillary blood with alveolar gas; 2) the uniform distribution of pulmonary blood flow and expansion of the alveolar-capillary surface area; and 3) the relatively low pulmonary vascular resistance experienced during heavy exercise. Furthermore, a strong compensatory hyperventilation in heavy exercise ensures a high alveolar PO_2 (P_AO_2), which in turn hastens the *rate of equilibration* of alveolar gas with mixed venous blood (also see below). An additional mechanism here is the substantial capacity of the lymphatic system to drain the pulmonary interstitial fluid space, thereby preventing accumulation of pulmonary extravascular lung water in the face of increased water turnover in the lung during exercise (12). Of course, the lung is not a perfect gas exchanger. Note that the alveolar to arterial PO_2 difference actually increases 2.5- to 3-fold from rest to exercise, most likely because not quite all of the right heart cardiac output comes in contact with alveolar gas and because $\dot{V}A:\dot{Q}c$ (alveolar ventilation:perfusion) distribution throughout the lung is not perfectly uniform and in fact even becomes slightly less uniform during moderate to heavy exercise (23, 24).

FAILURE OF HOMEOSTATIC CONTROL BY THE PULMONARY SYSTEM

Examples in pathophysiology. Few patients with chronic pulmonary disease tolerate exercise well. For example, because of the substantial reserves of the lung and chest wall significant degrees of chronic airway obstruction, loss of elastic recoil (such as in interstitial lung diseases), reduction of the pulmonary vascular bed and gas exchange surface area (as in emphysema), and even some degree of right to left "shunt" of mixed venous blood into the systemic circulation may be present before arterial blood gases become abnormal or even shortness of breath is experienced in the resting state. However, even mild intensities of exercise commonly cause: 1) CO_2 retention in the patient with airway obstruction and lung hyperinflation because the

increased ventilatory demand cannot be met when resistance to airflow is high and/or the use of the diaphragm is restricted because of its shortened length and reduced radius of curvature; 2) arterial hypoxemia in the patient with even a small shunt because of a reduced mixed venous O_2 content; 3) pulmonary hypertension and hypoxemia in the patient whose limited pulmonary vascular bed cannot expand coincident with an increased pulmonary blood flow; and 4) dyspnea in the patient with increased pulmonary impedance because the work and energy expenditure required by the respiratory muscles to produce the normal hyperpnea of exercise is excessive and thus an inappropriate development of muscle tension is now somehow "sensed" by the higher CNS (37). In short, there are simply markedly fewer options for the control system to explore in the strategy of maintaining a "minimum cost" of achieving exercise hyperpnea when it is faced with a diseased effector organ which presents little in the way of reserve function in order to meet augmented demands.

Effects of alien environments. Even the healthy untrained pulmonary system also experiences less than ideal responses to exercise outside of our native sea level, temperate environment. In the hypoxia of moderately high altitude (>12,000 ft) arterial PO_2 can be maintained at resting levels during even high intensity exercise, but the cost is substantial in terms of the marked degree of hyperventilation and thus ventilatory work required to maintain alveolar PO_2 sufficiently high (13). At higher altitudes (>14,000 ft) even during only moderately heavy exercise breathing frequency commonly exceeds 70–80 breaths per minute and $PaCO_2$'s are in the mid-teens—but even this extra hyperventilatory response doesn't prevent marked exercise-induced arterial hypoxemia at these higher altitudes (13, 50). The combination of hypoxia and exercise provides powerful synergistic stimuli to breathe which probably override any attempt of proprioceptive feedback control to minimize ventilatory work in these situations. This was dramatically demonstrated by reports of the final few hundred meters of ascent to Mount Everest where alveolar PO_2 is in the mid 20's and $P_ACO_2 < 10$ mm Hg (57); the ventilatory response to exercise was best characterized as 4–5 vital capacity breaths per step. Quite the opposite response to exercise is observed in high air density, hyperbaric environments where the work of breathing at any given $\dot{V}O_2$ is protected (i.e., it stays the same as in the normobaric environment) despite higher resistance to airflow; but this occurs at the expense of alveolar hypoventilation and marked respiratory acidosis (31, 32).

Finally, a highly inefficient ventilatory response may occur to prolonged heavy exercise in trained or untrained subjects running in hot, humid environments (Fig. 6) (30). Note that at the beginning of a 15-mile

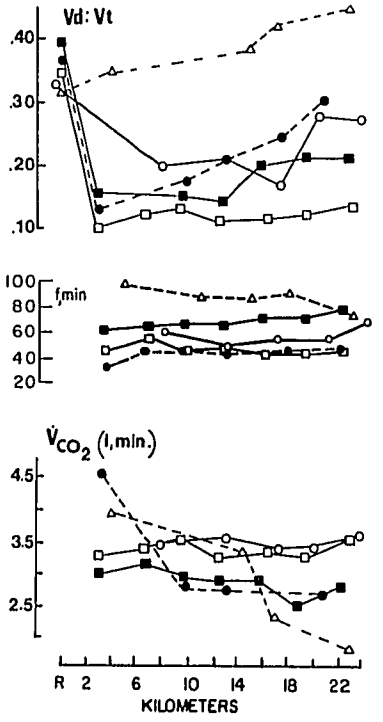

Figure 6—Tachypneic response in humans to long-term exercise under conditions of normal environmental heat and humidity (——) and in a hot humid environment (– – –) (see text).

(24-km) road race the ventilatory response included the normal reduction in the fraction of dead space which accompanied the increase in tidal volume; but as exercise continued, especially under hot, humid conditions, breathing frequency increased, dead space ventilation increased, and $PaCO_2$ commonly even rose slightly despite the rising overall minute ventilation (30). This inefficient tachypneic pattern of response seemed to occur almost independently of any of the usually important drives to breath such as CO_2 production, which actually fell in many cases as tachypnea proceeded, or arterial pH, which remained constant at normally mildly alkaline values. This response is in part reminiscent of the panting animal such as the dog during exercise in the heat. However, the major species difference here is that the dog benefits greatly from the considerable energy expended in panting by controlling his brain temperature while maintaining fairly normal arterial PCO_2 (2, 29), whereas the human benefits little if at all in terms of heat dissipation and experiences only a highly inefficient tachypneic pattern, increased ventilatory work, and often dyspnea; and if the accompanying hypocapnia is sufficient the human will experience substantial, sustained reductions in cerebral blood flow (16).

A preliminary conclusion to the examples cited thus far is that the suitability of the healthy pulmonary system for exercise is limited, in that the multiple demands imposed by exercise in some alien environ-

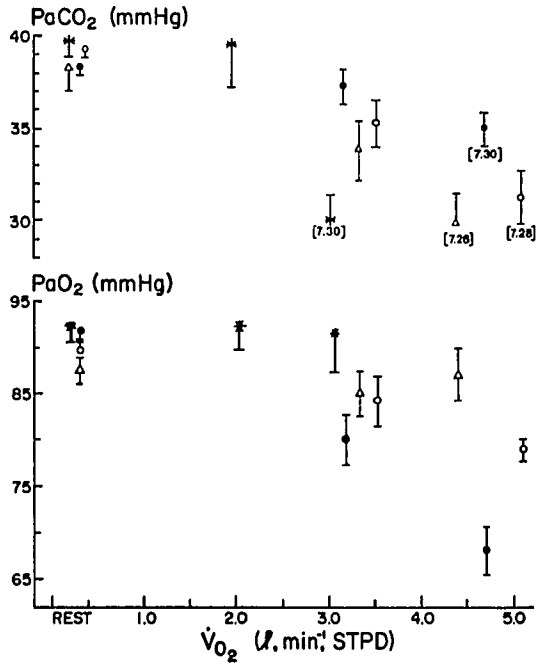

Figure 7—Regulation of arterial blood gases and acid-base status in healthy young adult males—untrained (*) and trained (△, ●, ○)—during sub-maximum and maximum treadmill running. Bars, SD.

ments and in the presence of most types of chronic pulmonary disease erode the *efficiency* of the ventilatory response, cause *compromises* to be made among segments of the control system, thereby sacrificing homeostasis, and in some cases even exceed the *capacity* of the ventilatory pump and the gas exchange apparatus. But these examples are clearly extreme, and most are even beyond the boundaries of what might be termed physiological. Let us turn now then to the more relevant example of the failure of homeostasis experienced at high exercise intensities by some highly trained athletes.

The highly trained. Figure 7 compares arterial blood gases during submaximal and maximal exercise in untrained subjects ($\dot{V}O_{2max}$ = 37 to 47 ml·kg^{-1}·min^{-1}) and in three groups of trained runners ($\dot{V}O_{2max}$ = 58 to 82 ml·kg^{-1}·min^{-1}) (15, 17). At the level of $\dot{V}O_{2max}$ the key differences between trained and untrained are summarized in Figure 7. The untrained group and one of the three athletic groups maintained PaO_2 as they widened their alveolar to arterial oxygen difference ($A\text{-}aDO_2$) but reduced $PaCO_2$ and therefore increased alveolar PO_2 sufficiently to maintain arterial PO_2 within 10 mm Hg of resting values; whereas the remaining two athletic groups, especially one of the groups, reduced PaO_2 because they failed to hyperventilate sufficiently and because they excessively widened their alveolar to arterial O_2 difference.

The potential causes underlying the absence of compensatory hyperventilation in many of these highly trained subjects are complex and thus far have received little attention. First, we can rule out the absence of sufficient chemical stimuli, as arterial lactate concentrations were in the 12 to 16 meq·l^{-1} range, arterial pH was substantially acid (Fig. 7), and of course arterial PO_2 was reduced. Additional potential chemoreceptor stimuli included increased circulating norepinephrine to 20 to 25 times resting values (13). The ventilatory control system appears, then, to ignore these extra and usually very powerful combinations of ventilatory stimuli, and this impression was confirmed by noting: 1) that over time (up to 6 min) at a fixed heavy exercise intensity, $\dot{V}_E$ and $PaCO_2$ failed to respond to increasing acidosis, circulating catecholamines, and hypoxemia (15); 2) that repeat trials of heavy exercise in the same subjects often yielded quite different metabolic acidosis (especially when glycogen depletion occurred) but caused no change in the ventilatory response (17); and 3) that imposing hyperoxia or (more) hypoxemia (via changing inspired O_2) had relatively little influence on the ventilatory response (15, 17). More specific data are needed concerning the responsiveness of *peripheral* chemoreceptors. Simply on the basis of the potential stimuli measurable in arterial blood, the magnitude of this chemoresponsiveness probably plays some significant role in determining interindividual differences in the amount of hyperventilation.

The hyperbolic relationships between $\dot{V}_E$ and $PaCO_2$ (or alveolar PO_2) at varying $\dot{V}CO_2$ require markedly different ventilatory requirements of the trained vs untrained in achieving comparable hyperventilation in heavy exercise (Fig. 8). For example, the untrained individual with a $\dot{V}CO_2$ of 3 l·min^{-1} requires a $\dot{V}_E$ of 110 to 120 l·min^{-1} to achieve $PaCO_2$ of 30 mm Hg and alveolar PO_2 of 115 to 120 mm Hg, the latter ensuring protection from arterial desaturation during exercise; whereas the athlete at 5 to 6 l·min^{-1} $\dot{V}CO_2$

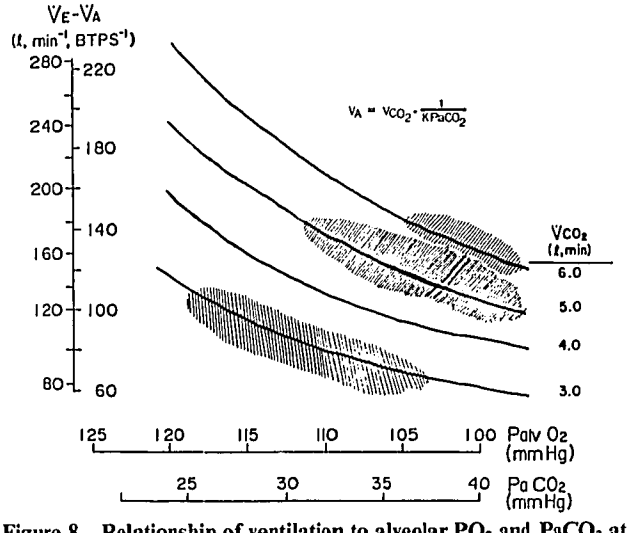

Figure 8—Relationship of ventilation to alveolar PO_2 and $PaCO_2$ at increasing levels of steady-state $\dot{V}CO_2$. The shaded areas show the range of ventilatory responses achieved by the trained and untrained at varying levels of maximum $\dot{V}CO_2$. (Vd:Vt assumed = 0.20). This concept is adapted from Wasserman and Whipp (53).

needs $\dot{V}_E$ in excess of 200 $l \cdot min^{-1}$ to achieve this same compensatory protection. These extreme ventilatory demands imply that maximum flow limitations might be approached, and a true mechanical limitation or even respiratory muscle fatigue may explain the absence of compensatory hyperventilation in some of these athletes. Additional supportive data for these ideas are that maximum volitional expiratory flow:volume limits may be exceeded in some athletes at very high exercise intensities (27); and reducing the mechanical impedance by breathing $He:O_2$ causes immediate and substantial hyperventilation in all of these athletes (15, 17). However, these data are incomplete. We lack sufficient details comparing mechanics of the lung and chest wall in subjects who do vs those who do not show compensatory hyperventilation. We postulate that lack of this compensation occurs when respiratory motor output or drive is not augmented sufficiently at these high exercise intensities because of feedback inhibition from chest wall to brain stem. The result is that respiratory muscle pressure development increases in proportion to, but not out of proportion to, increasing $\dot{V}CO_2$, and respiratory muscle fatigue is spared; but of course this occurs at the expense of arterial blood gas homeostasis. A feedback inhibition of ventilatory output has been shown to occur in the anesthetized dog whose diaphragm has been fatigued via artificial mechanical loads or shock (34). The apparent (involuntary) inhibition of expiratory effort during heavy exercise (Fig. 3) is an example of proprioceptive control over force development by respiratory muscles which indirectly spares fatiguing efforts by avoiding dynamic airway compression. We do not know if inspiratory muscle force development might also be under similar feedback control, but the helium breathing (unloading) effects on diaphragmatic EMG (Fig. 4) did demonstrate that some type of mechanical "load" presented by the normal impedance, even in the healthy lung, is being sensed by inspiratory muscles and is partially compensated during submaximal exercise.

An abnormal widening of the alveolar to arterial O_2 difference was the other major cause of the hypoxemia in these athletes (Table 1). Note that the A-aDO_2 is increased in maximal exercise over the resting state in *all* groups, whether PaO_2 was maintained *or* hypoxemia occurred. Most of the widened A-aDO_2 in maximal exercise was found (using the multiple inert gas technique) to be due both to an imperfect $\dot{V}A:\dot{Q}c$ distribution which widened slightly during exercise and to the persistence of a small shunt of venous blood via the bronchial and the thebesian circulation, in the face of a markedly reduced mixed venous O_2 content (24, 50).[2]

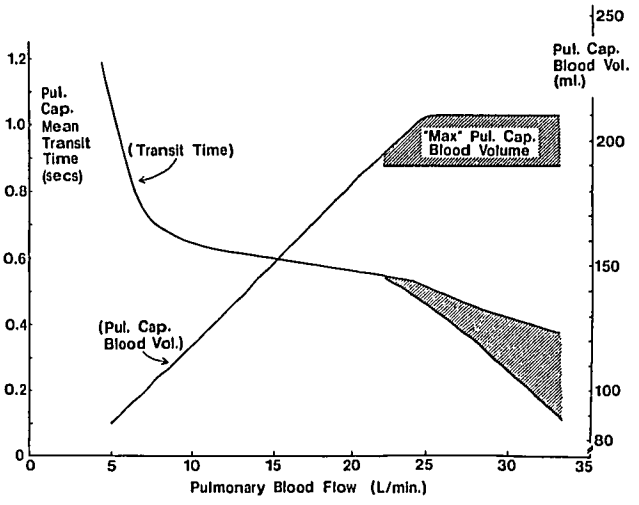

Figure 9—Relationship of increasing pulmonary blood flow ($\dot{Q}c$) within increasing exercise load to the expansion of the pulmonary capillary blood volume (Vc) and the effect of this relationship on average red cell transit time through the lung (mean transit time = capillary blood volume/pulmonary blood flow). We propose that Vc achieves maximum morphological expansion at ~2.5 the resting value; thereafter as exercise and $\dot{Q}c$ increase further, transit time will fall precipitously. A possible range of such times is shown by the shaded area.

We propose that the reason for this *extra* widening of the A-aDO_2 in the hypoxemic athlete is that pulmonary blood flow is capable of increasing beyond the point at which pulmonary capillary blood volume has reached its maximum morphological limits; consequently the transit time of the red blood cell through the pulmonary capillary bed falls precipitously at these higher exercise intensities (Fig. 9). What minimum transit time is sufficient for equilibration of mixed venous blood with alveolar gas? This is not a fixed time; rather it has been demonstrated (52) that at any given diffusion distance (and diffusion capacity) the rate of equilibration of $P\bar{v}O_2$ with P_AO_2 will depend critically on the "effective slope" of the HbO_2 dissociation curve between end-pulmonary capillary blood ($\acute{c}$) and mixed venous blood ($\bar{v}$) and (C) content.

$$\text{"Effective slope"} = \frac{C\acute{c}O_2 - C\bar{v}O_2}{P\acute{c}O_2 - P\bar{v}O_2}$$

(where $P2c'O2 = P_AO2$). Thus, the lower the mixed venous PO_2 and the closer the alveolar PO_2 is to the steeper portion of the HbO_2 dissociation curve the greater the "effective slope" and the longer the transit time required for equilibration. At $\dot{V}O_{2max}$ in our runners, $P\bar{v}O_2$ would be very low (~12–15 mm Hg or $C\bar{v}O_2$ ~1.5–2 ml O_2 per 100 ml). When combined with the relatively low alveolar PO_2 in those runners who showed little hyperventilation, about 30% longer transit times

[2] Torre Bueno et al. (50) recently estimated that even at exercise levels requiring only 3–3.5 $l \cdot min^{-1}$ $\dot{V}O_2$ (where PaO_2 is maintained within 10 mm Hg of resting levels,) less than one-half of the observed A-aDO_2 was accounted for by non-uniformity of $\dot{V}_A:\dot{Q}c$ distribution. They attributed the remainder to failure of diffusion equilibrium and argued that only a negligible portion of the A-aDO_2 would be due to shunt.

TABLE 1. Causes of exercise-induced hypoxemia (untrained vs trained vs trained).

	3 l·min^{-1} $\dot{V}O_{2max}$†		5 l·min^{-1} $\dot{V}O_{2max}$†		
Alveolar PO_2 (mm Hg)	120	Imperfect $\dot{V}A$:$\dot{Q}c$ distribution + 1% veno-arterial shunt	115	105	No compensatory hyperventilation + $\dot{V}A$:$\dot{Q}c$ non-uniformity + shunt + diffusion disequilibrium
Arterial PO_2 (mm Hg)	90		87	60*	
Alv.-art. O_2 difference (mm Hg)	30		28	45	

* Note that arterial PO_2 is 25–30 mm Hg less in this group than in the other trained group or in the untrained group. About one-half of this hypoexmia is due to a lower alveolar PO_2 (less hyperventilation) and one-half is due to a wider alveolar to arterial PO_2 difference (a diffusion disequilibrium in end-pulmonary capillary blood added to the "normally"occurring $\dot{V}_A$:$\dot{Q}c$ non-uniformity and small veno-arterial shunt).
† Other pertinent estimates not shown here include $\dot{Q}c$ and mixed venous O_2 content, which would be about 18–20 l·min^{-1} and 5 ml O_2, 100 ml, respectively, at 3 l·min^{-1} $\dot{V}O_2$ and 28–32 l·min^{-1} and 1–3 ml O_2 (100 ml at 5 l·min^{-1} $\dot{V}O_2$).

in the pulmonary capillary would be required to reach equilibration with alveolar gas than in those subjects with more hyperventilation and higher alveolar PO_2 at similar $\dot{V}O_2$ and $\dot{Q}c$ (Table 1).

Thus, we think it likely that the markedly shortened transit *time* in combination with the reduced *rate* of equilibration would cause a significant diffusion disequilibrium for O_2 at the end of the pulmonary capillary in those athletes with a combination of high cardiac output, maximum pulmonary capillary blood volume, and no or little hyperventilation.

One additional factor interfering with $\dot{V}A$:$\dot{Q}c$ distribution and alveolar to arterial gas exchange might be accumulation of extra-vascular lung water under conditions in which very high pulmonary capillary pressures would increase plasma water exudation into the interstitial fluid space in excess of lymphatic drainage capabilities. Pulmonary arterial "wedge" pressures have been reported in excess of 15–20 mm Hg in a few healthy subjects at maximum exercise (25).

CHRONIC ADAPTABILITY

Pulmonary system adaptability. Exercise-induced arterial hypoxemia and the absence of a significant compensatory hyperventilation in the highly trained athlete imply that critical aspects of the pulmonary control system have not adapted appropriately to the increased metabolic demands. This implication seems inconsistent with the concepts of organ system adaptation put forward by Weibel (54, 55). Using data gathered across species of varying body size these investigators documented close logarithmic relationships between increases in $\dot{V}O_{2max}$ and increased mitochondrial volume in limb, respiratory, and cardiac muscles. Noteworthy here is the fact that very high metabolic rates (in smaller animals) coincided with very high breathing frequencies and caused adaptation in mitochondrial volumes in the diaphragm of such magnitude that they approached those seen even in the myocardium of heavier animals with lower metabolic rates and breathing frequencies. Maximum diffusion surface or capacity of the lung also was shown to increase with increasing body weight, even out of proportion to the increase in $\dot{V}O_{2max}$. Similar adaptive capabilities of the pulmonary system to increased metabolic demand were also shown by comparing the lungs or respiratory muscles between animals of similar body weight but who have markedly different habitual physical activity (example: cow vs horse; dog vs human).

The architecture of the lung's gas exchange apparatus also demonstrates substantial chronic adaptation upon exposure to chronic oxygen lack. In humans this is shown by the 2–3-fold increase in pulmonary diffusion capacity and pulmonary capillary blood volume and the narrowed alveolar to arterial O_2 difference during exercise in the native and long-term (i.e., greater than 2 yr) resident of high altitude (11). This enhanced capability for alveolar to arterial O_2 transport is especially important to exercise in a hypoxic environment, because the resident also avoids the marked tachypneic hyperventilatory response to exercise in hypoxia experienced by the sojourner, thereby obviating the increased ventilatory work and accompanying dyspnea without sacrificing arterial O_2 content. The real gold standard of pulmonary adaptation in hypoxia is the so-called "cross-current" gas exchange system in birds, which has achieved such perfection in its efficiency that geese are capable of flying in excess of 30,000 ft altitude with an arterial PO_2 which is only 1 or 2 mm Hg less than their inspired PO_2 (5). Remarkable, "*extra*-pulmonary" gas exchange also occurs in these birds so that blood perfusing the evaporative surfaces in their mouth, nose, and eyes serves not only to cool but also to directly oxygenate blood flowing to the brain as it passes through its cephalic vascular heat exchanger (4).

Respiratory muscles are also capable of undergoing true structural adaptation to chronic "overload" within different species. Examples of this include the increase in respiratory muscle strength and endurance in humans, at least as determined by maximum volitional

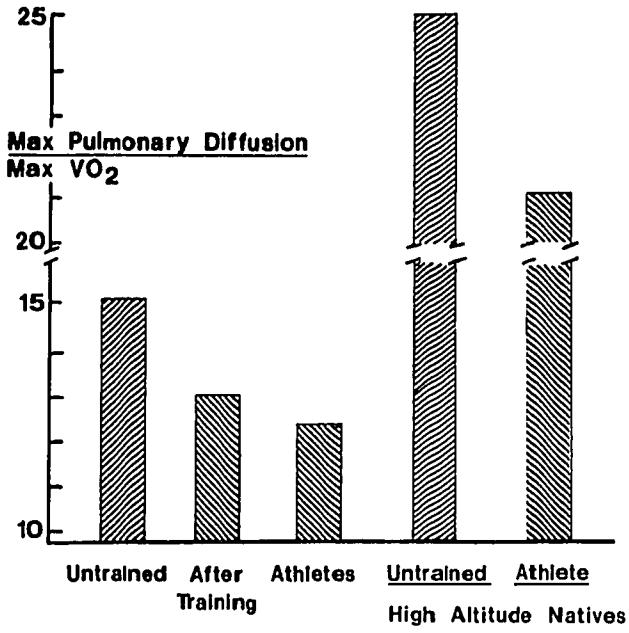

Figure 10—Effects of chronic physical training and/or the trained state on the relationship of maximum pulmonary diffusion capacity (for CO, i.e., D_LCO) to $\dot{V}O_{2max}$ ($l \cdot min^{-1} \dot{V}O_2/ml \cdot min^{-1} \cdot mm\ Hg^{-1}$ D_LCO) (see text).

tests, as a result of specific training of the respiratory muscles by resistance breathing exercises (39); and the substantial increase in oxidative capacity of rat diaphragm induced by artificially increasing airway resistance by tracheal stenosis over many weeks (36).

So, given stimuli of sufficient intensity, specificity, and duration, the pulmonary control system is indeed capable of quite extensive and even remarkable morphological adaptation, which is sometimes critical to survival in alien environments. The problem to the human athlete is that these types of adaptation do not seem to apply to the effects of physical training within a species. This is made most clear with the gas exchange function of the human lung as shown in Figure 10 which relates $\dot{V}O_{2max}$ to the maximum pulmonary diffusion capacity (D_{Lmax}) as an estimate of the overall maximum usable gas exchange surface area in the lung. Note that from trained to untrained the $\dot{V}O_{2max}$ increases, but the maximum diffusion changes little if at all (6, 44). Similarly in chronic residents of high altitude, the maximum diffusion capacity is higher, but in the athletic residents diffusion is not increased in proportion to $\dot{V}O_{2max}$ and once again any "reserve" for gas exchange capability in the untrained is eroded with the training process (13). A similar dissociation of $\dot{V}O_{2max}$ and D_{Lmax} holds for the sedentary sojourner to high altitude who is able to increase his $\dot{V}O_{2max}$ back towards sea level values during an 8-wk period of intense training in hypoxia but undergoes no true "adaptation" at the pulmonary level in this short time period (13). We know less about the "trainability" of the chest wall, but limited data in rats show that any change in oxidative capacity of the respiratory muscles which occurs with prolonged training was quite small and substantially less than that obtained in limb locomotor muscles (41). There is a theoretical limit to the utility of some types of changes in respiratory muscle function; for example, the ability to generate high rates of expiratory flow is clearly more a function of airway compressibility at low lung volumes than it is of the pressure generating capability of expiratory muscles (Fig. 4).

Finally, a contrast of training effects on limb vs lung may be seen in vascular volumes. The capability to expand the capillary volume of the organ's vascular bed coincident with rising blood flow is critical to preserving red cell transit time, and this principle holds both for the lung in terms of alveolar-capillary equilibrium (see above) and in working skeletal muscle in terms of O_2 off-loading and the widening of the arterial-venous O_2 difference (46). Two major differences in this regard are evident between the organ systems: first, the limbs don't receive all of the increased cardiac output—thus the threat to transit time is not as great as in the lung; and secondly, the limb skeletal muscle capillarity density undergoes substantial adaptative growth in the physically trained.

Dominance of locomotor adaptations in the equine athlete. A quite different form of an apparent lack of pulmonary adaptation to increased metabolic demand may be seen in the thoroughbred horse. Literally centuries of traditional forms of "genetic engineering" have produced an athlete capable of achieving running velocities which are more than 1½ times those of the fastest humans (~10 $m \cdot s^{-1}$ vs 16+ $m \cdot s^{-1}$) and, even more remarkable, of maintaining these velocities over more than 15 times the distance (100 vs ~1500+ m). It follows, then, that $\dot{V}O_{2max}$ in trained horses may approximate 150 $ml \cdot kg^{-1} \cdot min^{-1}$, and cardiac outputs in excess of 600 $l \cdot min^{-1}$ have been measured along with mixed venous PCO_2 in excess of 100 mm Hg, $P\bar{v}O_2$ below 15 mm Hg, and depletion of limb muscle ATP as much as 50% following repeated exhaustive running performances (48, 49).

At first glance the pulmonary system appears to be ideally suited to matching these Herculean requirements. The horse, along with other habitually active cursorial animals, appears to have an appropriately enlarged alveolar-capillary surface area (54). More importantly, the galloping thoroughbred links breathing frequency 1 for 1 with stride frequency, as expiration always occurs when the forelegs are weight-bearing and inspiration occurs as the trunk is thrust forward by the hind limbs (7, 8). Much has been made of the remarkable suitability of this locomotor:respiratory coupling to the athletic demands of the quadruped by emphasizing the efficiency of this coupling process in animals whose thorax muscles must serve not only ventilatory needs but also those of propulsion and a large share of

the animal's bodily support (8, 33). Thus, according to one comprehensive theory (7) as the forelegs strike the ground, thoracic gas volume during *expiration* is reduced both by the relaying of powerful ground forces to the rib cage via chest wall musculature and by shifting the abdominal contents or "visceral piston" forward against the diaphragm causing compression of the thorax; and with *inspiration* the anterior rib cage is enlarged by the same chest wall muscles which rotate the shoulder girdle forward and protract the forelimbs and also by extension of the head and neck, which is in turn linked by several muscle masses to the anterior end of the bony thorax.[3] Any additional neural control of these proposed actions remains largely unexplored, although a tight coupling of feedforward stimuli for both limb and respiratory muscle activation seems plausible (19).

Unfortunately, what appears to be a nearly ideally built and designed matching of extraordinary needs for both locomotion and gas exchange suffers from some of the same shortcomings we have discussed above for some human athletes. Thus, recent studies have shown that arterial hypoxemia is achieved in the galloping thoroughbred comparable to that seen in some human athletes. This hypoxemia in the horse also occurs in the absence of a significant compensatory hyperventilation in heavy exercise; furthermore, the thoroughbred actually *retains* very significant amounts of CO_2 (relative to the resting state) as $PaCO_2$, is in the range of 50–60 mm Hg in heavy exercise (2, 49). It appears, from limited data, as though the CO_2 retention (and low alveolar PO_2) rather than any abnormal widening of the alveolar to arterial oxygen difference is the major cause of the exercise induced arterial hypoxemia in the horse. The CO_2 retention must be linked to the obligatory association of breathing and stride frequency. First, these very high breathing frequencies cause higher dead space ventilation and therefore require greater overall ventilatory responses to match metabolic demand. According to the limited data available, tidal volume only achieves a maximum of about 30% of the vital capacity in the exercising horse; $\dot{V}_E$:$\dot{V}CO_2$ is very low and CO_2 retention develops (33). The limitations on tidal volume might be due to the very short times made available for inspiration and expiration: 1) to complete *expiration* (so that FRC is maintained at least at its normal resting volume) the required flow rate might exceed the maximum available flow at lower lung volumes; and 2) to achieve the necessary flow rates to complete *inspiration* in the allotted time may require a magnitude of pressure development and/or velocity of shortening which would lead to fatigue of the inspiratory muscles.

Achieving the same running velocity at greater stride length and lower frequency might be the preferred strategy for increasing tidal volume (and $\dot{V}_E$), but this approach may not achieve the same economy of locomotion (or breathing). Perhaps these speeds simply can't be achieved (neuromuscularly) at lower stride frequencies. These choices are available in the bipedal running posture in humans who also sometimes entrain breathing and locomotion but are not obligated to a strict 1:1 coupling (8). I emphasize the highly speculative nature of this idea, as even the most basic of measurements of flow:volume relationships, FRC, and lung and chest wall mechanics have not as yet been made in the galloping thoroughbred. Finally we note that this hypoxemia—especially when combined with a mixed (respiratory plus metabolic) acidosis—most certainly must limit these thoroughbreds' work capacity. Interestingly, the reduced arterial HbO_2 saturation would negate much of the increase in O_2 carrying capacity experienced by the horse during exercise secondary to the liberation of red blood cells from their splenic reserve.

SUMMARY

In summary, we have shown that the design of the pulmonary system from the architectural capacities of the lung parenchyma and respiratory muscles to the remarkable, multi-level neural integration of breathing pattern and respiratory muscle recruitment is clearly intended for the exercising state. Furthermore, the system shows remarkable capability for true adaptation, both phylogenetically and even within only a few generations within a species, when preservation of the organism's ability to survive and function is at stake. At the same time there are limits to the system's homeostatic capabilities, and these appear in instances other than the "usual" ones, where the capabilities for gas transport and utilization beyond the lung (i.e., by the cardiovascular and musculo-skeletal systems) surpass those of the lung and chest wall, such as during exercise in certain pulmonary disease states *or* in alien environments *or* in the highly trained. Exercise-induced hypoxemia in the thoroughbred horse is a different type of dominance of the superior locomotor control system, because their extraordinary capability to produce and sustain a very high limb velocity dictates requirements for airway flow rates which may surpass the mechanical capabilities of the lung and perhaps even the chest wall.

So this hypothesis does indeed suggest that the

[3] Bramble views this locomotor control over thoracic gas volume to be dependent upon a coordinated "piston:pendulum" type of action, i.e., horizontal shifts in abdominal contents + vertical shifting of the head and neck (7). Some years ago Michael Goldman also suggested, in a more rudimentary form, that perhaps the "sloshing of the guts" might have some bearing on exercise hyperpnea in humans. Both running humans and horses do show huge, transient increases in abdominal pressure just preceding and during the footplant (26).

healthy pulmonary system may become a so-called "limiting" factor to oxygen transport and utilization and to CO_2 transport and elimination, at least during short-term maximum exercise in the highly trained. On the one hand, the idea is especially appealing in a philosophical sense because of its conceptual tidiness and its confirmation of the premise that no organ system has limitless functional capacity; on the other hand, given the long list of our still untested speculations, we could use a bit more data.

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Address for correspondence: Dr. Jerome A. Dempsey, 504 N. Walnut St., Madison, WI 53705.

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